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Effects of Diazoxide Administration on Plasma Glucose, Insulin, and Lipids in von Gierke's Disease

GABRIEL SPERGEL

Fellow in Diabetes and Endocrinology
Clinical Metabolic Research Unit, The Jewish Hospital of Brooklyn
Brooklyn, N. Y.

Diazoxide, a nondiuretic thiazide, has been noted to cause hyperglycemia and has been used therapeutically in the treatment of the hypoglycemia associated with leucine sensitivity and insulinomata.

The mechanisms by which this drug induces hyperglycemia were studied during the treatment of a 12-year-old boy with type 1 glycogen storage disease and marked hyperlipemia.

1) Inhibition of the plasma immunoassayable insulin response to administered glucose was shown, as well as an increase of 30 to 70 mg./100 ml. in postprandial plasma

glucose levels. Oral glucose tolerance decreased during treatment with diazoxide. These changes in plasma glucose were not due to glycogenolysis, by virtue of the enzymatic defect present in this patient.

2) During treatment, skin xanthomata disappeared although plasma triglycerides rose. Serum cholesterol was unchanged while plasma-free fatty acids initially rose but subsequently spontaneously declined.

3) Analysis of serial oral glucose tolerance tests suggests that diazoxide inhibits hepatic glucose uptake, as part of its hyperglycemic action.

*Reevaluation of the Role of Calcium
in Corticotropin-Induced Lipolysis in Vitro*

MELVYN KLEIN

Fourth-Year Medical Student
State University of New York Downstate Medical Center
Brooklyn, N. Y.

The calcium-dependent nature of corticotropin (ACTH)-induced lipolysis *in vitro*, shown by Engel *et al.*, was reinvestigated. Epididymal fat tissue from fasted Wistar rats was incubated in Krebs-Ringer bicarbonate buffer. Incubated tissues and media were then analyzed for free fatty acid (FFA) release. The three hypotheses were examined, and the results of these investigations were:

1) *Calcium could reduce glucose entry into fat tissue and, by diminishing triglyceride synthesis, facilitate net lipolysis.* In the presence of 1 mg./ml. ethylenediamine tetra-acetate (EDTA) and 2 gm./100 ml. albumin, the lipolytic response to 1 µg./ml. ACTH was found to be dependent on the presence of added calcium, irrespective of the presence or absence of glucose in the medium.

2) *The lipolytic system activated by ACTH could require calcium to function.* EDTA suppressed ACTH-activated lipoly-

sis only in the presence of albumin: in its absence, EDTA was wholly without liposuppressive effect.

3) *Primary ACTH receptor sites might contain calcium whereas, under EDTA blockade, less specific sites (for example, sulfhydryl groups), could permit ACTH attachment to fat tissue.* In the presence of EDTA, inhibition of ACTH-induced lipolysis was logarithmically related to albumin concentration in the incubation media. Sulfhydryl-group blockade proved ineffective in inhibiting ACTH-activated lipolysis in the absence of albumin. Several high molecular weight polypeptides and carbohydrate polymers were substituted for albumin in the presence and absence of EDTA, but had no liposuppressive effect.

These experiments suggest that the role of calcium in ACTH-activated lipolysis is to permit or facilitate ACTH attachment to adipose tissue.

*Effects of Induced Hypokalemia on Carbohydrate Metabolism,
Free Fatty Acids, Tissue Potassium, and Glycogen in the Rat*

PHILIP SCHMIDT,* GABRIEL SPERGER,* AND ALAN G. STERN**

The Jewish Hospital of Brooklyn
Brooklyn, N. Y.

The relationship between the potassium ion and carbohydrate metabolism has been the object of renewed interest. An animal study was undertaken to correlate changes in plasma glucose, free fatty acids, and tissue glycogen with alterations in plasma and tissue potassium.

Forty-two male Wistar rats were divided into three groups and fed a low potassium diet for 2 weeks.

Group I: controls, saline injected for 7 days, diet supplemented with potassium.

Group II: DOCA injected for 7 days, no potassium supplementation.

Group III: Same as II but with potassium supplementation.

One week after the last injection, fasting animals were anesthetized and heart blood drawn for potassium, glucose, and FFA. An intracardiac injection of glucose (1 g./kg.) was given and tail blood sampled for glucose at 5-minute intervals for 30 minutes.

Two hours after glucose injection, heart blood was again collected for potassium, glucose, and FFA, the animal sacrificed, and tissue (muscle, liver, and epididymal fat pad) obtained for potassium and glycogen determinations.

1) Profound hypokalemia was established in Group II while normal serum potassium was maintained in Groups I and III.

2) Significantly, adipose tissue and liver showed no loss of potassium despite marked decreases in both plasma and muscle potassium in Group II.

3) Potassium depletion did not produce a significant change in glucose disappearance rate. Fasting and 2-hour glucose values, however, were significantly elevated in potassium-depleted animals.

4) Liver and muscle glycogen was significantly increased in the potassium-depleted animals.

5) Plasma FFA (fasting and postglucose) were unaffected by potassium depletion.

*Fellow in Diabetes and Endocrinology, Clinical Metabolic Research Unit.

**Intern in Medicine.